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Professor Joshua Lederberg
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Dear Joshua:

It was good to see you in Orlando earlier this month and to hear your excellent talk. Your presentation was stimulating, reflective and full of insight. We are all fortunate that you have undertaken a leading role in awakening the nation to the realities of infectious disease biology. From the conversations I had later, it was apparent that many IDSA members were highly appreciative of your remarks.

There was one topic which you raised about which our perceptions may differ. If I understood you correctly, you seemed to believe that it is not likely that selective pressure in the form of mortality from an infectious disease would significantly alter the susceptibility to that disease in the short period of one or two centuries or a few generations. How about diphtheria, a disease in which an epidemic began (or was first definitively described) in about 1812 and reached its peak mortality in Europe and North America in the 1870's? Mortality began to fall long before toxoid was widely applied (1929) and nearly disappeared by the 1960's, in spite of rather poor coverage of the population by toxoid? (There is just now a resurgence of diphtheria in Russia).

It has seemed to me for some time that the best explanation for this cyclic behavior is the elimination prior to child-bearing age of those most susceptible to the lethal effects of the toxin, leaving a more resistant population. This fits the high infection/case ratios in the tropical and subtropical regions and the marked differences in infection/case ratios in different human populations recorded during the pre-toxoid era. Of course, the rise and fall of diphtheria mortality could have been owing to changes in either virulence or infectivity of the organism, but I know of no evidence of either.

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I have been intrigued by the mysteries of diphtheria since the 1950's, and did a little work on it at that time. A reprint is enclosed. I would like to hear your opinion about the cyclic nature of diphtheria, and I would welcome the opportunity to discuss it with you some time. This letter hardly scratches the surface of this intriguing question, but I do think diphtheria is a disease which merits continuing attention, and about which a lot of very good data were collected in the first half of this century. In fact, I would say that Wade Hampton Frost's papers on diphtheria epidemiology rank second to none in dealing quantitatively with the natural history of an infectious disease.

Although diphtheria has become quite rare in the "developed" world, it would seem unwise to ignore its apparent passing. In fact, its virtual disappearance in some areas is all the more reason to study it. We may now have some genetic tools which could provide some answers. In addition, I think it is highly likely that the earlier studies of diphtheria could teach us a lot about the "new" diseases we are facing today.

With kindest regards,

Sincerely,

John P. Craig

enc: reprint